RLD INTELLECTUAL PROPERTY ORGANIZAT International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER TR

(51) International Patent Classification 7:		JNDER THE PATENT COOPERATION TREATY (PCT) (11) International Publication Number: WO 00/152
A61K 31/00	A2	(43) International Publication Date: 23 March 2000 (23.03.
(21) International Application Number: PCT/JP9 (22) International Filing Date: 10 September 1999 (1)		Osaka Factory, 1-6, Kashima 2-chome, Yodogawa-
(30) Priority Data: PP 5841 14 September 1998 (14.09.98)	8) A	(81) Designated States: BR, CA, CN, JP, KR, US, European pat (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, LU, MC, NL, PT, SE).
(71) Applicant (for all designated States except US): SAWA PHARMACEUTICAL CO., LTD. [JP/J] Doshomachi 3-chome, Chuo-ku, Osaka-shi, 541-8514 (JP).	Pl: 4_	Published
(72) Inventors; and (75) Inventors/Applicants (for US only): YAMA Nobuchika [JP/JP]; 17–10–303, Mukomotomachi I- Amagasaki-shi, Hyogo 661–0043 (JP). YAM Harumi [JP/JP]; 1882–26, Shimoinayoshi, Chiyod Niihari-gun, Ibaraki 315–0052 (JP). ISHI Takeshi [JP/JP]; 3–6–6–602, Kaminoshima-cho gasaki-shi, Hyogo 661–0014 (JP). JOHKI, Shigeru 2–1–13–1203, Koishikawa, Bunkyo-ku, Tokyo 11 (JP). SAKAI, Fumio [JP/JP]; 6–7, Ninomiya 2- Tsukuba-shi, Ibaraki 305–0051 (JP).	-chome AZAK Iamach KAWA , Ama [JP/JP]	

(57) Abstract

A new use of immunosuppressant for treating or preventing MMP-medicated diseases is provided.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AΤ	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav	TM	Turkmenistan
BF	Burkina Faso	GR	Greece		Republic of Macedonia	TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
ВJ	Benin	ΙE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	· VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	zw	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's	NZ	New Zealand		
CM	Cameroon		Republic of Korea	PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		





INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATIO

(51) International Patent Classification 7:			TOPER THE PATENT COUPERATION	ON TREATY (PCT)
1	1	_ '	(11) International Publication Number:	WO 00/15208
A61K 31/435, 38/13	A.	_	(43) Internati nal Publication Date:	
			de la	23 March 2000 (23.03.00)
(21) International Application Number:	PCT/JP99/04	4978	(74) Agent: TABUSHI, Eiji; Fujisawa	Pharmaceutical Co., Ltd.

(22) International Filing Date:

10 September 1999 (10.09.99)

14 September 1998 (14.09.98)

(71) Applicant (for all designated States except US): FUJI-SAWA PHARMACEUTICAL CO., LTD. [JP/JP]; 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka

541-8514 (ЈР). (72) Inventors; and (75) Inventors/Applicants (for US only): YAMAMOTO, Nobuchika [JP/JP]; 17-10-303, Mukomotomachi 1-chome,

Amagasaki-shi, Hyogo 661-0043 (JP). YAMAZAKI, Harumi [JP/JP]; 1882-26, Shimoinayoshi, Chiyodamachi, Niihari-gun, Ibaraki 315-0052 (JP). ISHIKAWA, Takeshi [JP/JP]; 3-6-6-602, Kaminoshima-cho, Amagasaki-shi, Hyogo 661-0014 (JP). JOHKI, Shigeru [JP/JP]; 2-1-13-1203, Koishikawa, Bunkyo-ku, Tokyo 112-0002 (JP). SAKAI, Fumio [JP/JP]; 6-7, Ninomiya 2-chome,

Tsukuba-shi, Ibaraki 305-0051 (JP).

Osaka Factory, 1-6, Kashima 2-chome, Yodogawa-ku, Osaka-shi, Osaka 532-8514 (JP).

(81) Designated States: BR, CA, CN, JP, KR, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published

With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(88) Date of publication of the international search report: 13 July 2000 (13.07.00)

(54) Title: NEW USE OF IMMUNOSUPRESSANTS FOR MMP-MEDIATED DISEASES

(57) Abstract

,

(30) Priority Data:

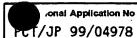
PP 5841

A new use of immunosuppressant for treating or preventing MMp-medicated diseases is provided. The preferred immunosuppressants are tacrolimus, cyclosporing A or 33-epi-chloro-33-desoxyascomycin (pimecrolimus). Particularly, preferable MMP-mediated diseases are the diseases or conditions caused by gelatinase and/or collagenase, and/or inflammatory diseases concerned with gelatinase; such as arthritis (e.g., osteoarthritis, rheumatoid arthritis, etc.), cerebral diseases (e.g., stroke, etc.), tissue ulceration (e.g., corneal, epidermal and gastriculceration, etc.), abnormal wound healing, periodontal diseases, bone diseases (e.g., Paget's diseases, osteoporosis, etc.), tumor growth, tumor metastasis or invasion, HIV-infection, decubitus, decubitis ulcer, restenosis, epidermolysis bullosa, sepsis, septic shock, neoplasm, psoriasis, neovascularization and multiple sclerosis.

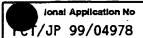
FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

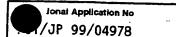
AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
ΑZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav	TM	Turkmenistan
BF	Burkina Faso	GR	Greece		Republic of Macedonia	TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
СН	Switzerland	KG	Kyrgyzstan	NO	Norway	zw	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's	NZ	New Zealand		
CM	Cameroon		Republic of Korea	PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		



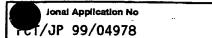
		ļ ř	C1/JP 99/049/8
A CLASSI IPC 7	FICATION OF SUBJECT MATTER A61K31/435 A61K38/13		
According to	o International Patent Classification (IPC) or to both national classific	eation and IPC	•
B. FIELDS	SEARCHED		
Minimum do IPC 7	cumentation searched (classification system followed by classification $A61K$	ion symbols)	
	tion searched other than minimum documentation to the extent that		
Electronic d	ata base consulted during the international search (name of data ba	ise and, where practical, se	arch terms used)
C. DOCUM	ENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the re-	levant passages	Relevant to claim No.
X	KATO, TAKASHI: "Effect of immunosuppressant drug (FK 506 as cyclosporin) on gingival fibroble NIPPON SHISHUBYO GAKKAI KAISHI (37(2), 211-223,1995, XPO00905248 abstract	asts" 1995),	1-9
X	TOCCI, MICHAEL J. ET AL: "The immunosuppressant FK506 selective inhibits expression of early T coactivation genes" J. IMMUNOL. (1989), 143(2), 718-2000906772 abstract	ell	1-9
X Furth	ner documents are listed in the continuation of box C.	Patent family me	nbers are listed in annex.
"A" docume consid "E" earlier of filing difficult docume which i citation "O" docume other n "P" docume later th	nt which may throw doubts on priority claim(s) or is cited to establish the publication dats of another in or other special reason (as specified) and referring to an oral disclosure, use, exhibition or means and published prior to the international filing date but can the priority date claimed	or priority date and no cited to understand the invention "X" document of particular cannot be considered involve an inventive seemed of particular cannot be considered document is combined in the art. "&" document member of the combined in the art.	
	May 2000	19/05/200	international search report
	nailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2	Authorized officer	-
	NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.	A. Jakobs	



		TeT/JP 99/04978
C.(Continu	ation) DOCUMENTS CONSIDERED TO BE RELEVANT	
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to daim No.
x	ARITA, C. ET AL: "Inhibition by FK506 of established lesions of collagen-induced arthritis in rats" CLIN. EXP. IMMUNOL. (1990), 82(3), 456-61, 1990, XP000904902 abstract	1-9
X	KOCH, K. ET AL: "CP-123,369: a potent, orally active immunosuppressive agent" INFLAMMATION RES. (1995), 44(SUPPL. 2), S183-S184,1995, XPO00904905 the whole document	1-9
X	SUGIYAMA, EIJI ET AL: "FK506, an immunosuppressant, partially inhibits interleukin 6 production by adherent rheumatoid synovial cells" J. RHEUMATOL. (1994), 21(9), 1597-601, 1994, XP000904906 abstract	1-9
X	GRIFFITHS, R. J. ET AL: "Characterization of passively transferred antigen arthritis induced by methylated bovine serum albumin in the rat: effect of FK 506 on arthritis development" AGENTS ACTIONS (1992), 36(1-2), 146-51, 1992, XP000904904 abstract	1-9
X	ZENIYA, AKIRA ET AL: "Anti- ulcer effect of FK 506, immunosuppressive agent, in rats" J. GASTROENTEROL. (1994), 29(3), 383-4, 1994, XP000904975 the whole document	1-9
x	WO 91 17754 A (FUJISAWA PHARMACEUTICAL CO) 28 November 1991 (1991-11-28) abstract page 2, line 5-29 page 5, line 1 -page 11, line 11; claims 1-19	1-9
X	KARASHIMA, TADASHI ET AL: "FK 506 and cyclosporin A inhibit growth factor-stimulated human keratinocyte proliferation by blocking cells in the GO/G1 phases of the cell cycle" J. DERMATOL. SCI. (1996), 12(3), 246-254, 1996, XP000904978 abstract	1-9



C (Continue		JP 99/04978
Category •	ation) DOCUMENTS CONSIDERED TO BE RELEVANT	
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to daim No.
X	MROWIETZ, U. ET AL: "The novel ascomycin derivative SDZ ASM 981 is effective for psoriasis when used topically under occlusion" BR. J. DERMATOL. (1998), 139(6), 992-996, 1998, XP000904979 abstract; figure 1	1-7
K	BUTCHER, STEVEN P. ET AL: "Neuroprotective actions of FK506 in experimental stroke: in vivo evidence against an antiexcitotoxic mechanism" J. NEUROSCI. (1997), 17(18), 6939-6946, 1997, XP000904977 abstract	1-9
	INABA, HIROYUKI ET AL: "Effect of indomethacin and tacrolimus hydrate on the healing process of experimental gastric ulcers of rats created by mucosal resection: course of changes in the interleukin-1.beta. (IL-1.beta.) expression" SEI MARIANNA IKA DAIGAKU ZASSHI (1998), 26(5), 555-563,1998, XP000905128 abstract	1-9
	SANDBORN, WILLIAM J.: "Preliminary report on the use of oral tacrolimus (FK506) in the treatment of complicated proximal small bowel and fistulizing Crohn's disease" AM. J. GASTROENTEROL. (1997), 92(5), 876-879, 1997, XP000905061 abstract	1-9
	HISANAGA ET AL: "Implication of nitric oxide synthase activity in the genesis of water immerstion-stress induced gastric lesions in rats: the protective effects of FK-506" ALIMENTARY PHARMACOLOGY & THERAPEUTICS, GB, BLACKWELL SCIENTIFIC PUBLICATIONS LTD., CAMBRIDGE, vol. 10, no. 10, 1996, pages 933-940-940, XP002108980 ISSN: 0269-2813	1-9
	wo 98 11908 A (BRITISH BIOTECH PHARM; WOOD LARS MICHAEL (GB); WRIGHT ANNETTE (GB)) 26 March 1998 (1998-03-26) abstract page 6, paragraph 4 -page 8, paragraph 2 page 15, paragraph 2; claims 1-8	1-9
	-/	



		7CT/JP 99/04978
	ation) DOCUMENTS CONSIDERED TO BE RELEVANT	
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 93 18048 A (PFIZER) 16 September 1993 (1993-09-16) abstract page 2, line 10 -page 5, line 23	1-7
X	WO 93 18050 A (PFIZER) 16 September 1993 (1993-09-16) page 2, line 11 -page 6, line 10	1-7
X	DE 43 29 503 A (GALENIK LABOR FREIBURG GMBH) 2 March 1995 (1995-03-02) abstract; claims 1-6	1-9
X	US 5 352 671 A (BAUMANN KARL ET AL) 4 October 1994 (1994-10-04) abstract column 25, line 49 -column 26, line 60; example 66A column 1, line 5	1-9
		·



mational application No.

PCT/JP 99/04978

Box	Observations where certain claims were found unsperchable (Continuation of the state)	_
	Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)	_
This Inte	mational Search Report has not been established in respect of certain claims under Articl 17(2)(a) for the following reasons:	
	Claims Nos.: 4,6,9 because they relate to subject matter not required to be searched by this Authority, namely:	
	Remark: Although claims 4, 6, 9 are directed to a method of treatment of the human/animal	
_	body, the search has been carried out and based on the alleged effects of the compound/composition.	
2 X	Claims Nos.:	
	Decause they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically: See FIRTHED INFORMATION SHEET DOT/TOA/OLO	
·	See FURTHER INFORMATION SHEET PCT/ISA/210	
	Claims Nos.:	
	ecause they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).	
Box II	bservations where unity of invention is lacking (Continuation of Item 2 of first sheet)	_
This Interna	ational Searching Authority found multiple inventions in this international application, as follows:	-
. —		
1. As	all required additional search fees were timely paid by the applicant, this International Search Report covers all archable claims.	
a 🗆		
2. As	all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment any additional fee.	
		I
3. As	only some of the required additional search fees were timely paid by the applicant, this International Search Report	I
w.	ers only those claims for which fees were paid, specifically claims Nos.:	l
4. No i	required additional search fees were timely paid by the applicant. Consequently, this International Search Report is ricted to the invention first mentioned in the claims; it is covered by claims Nos.:	ĺ
	The claims in the claims; π is covered by claims Nos.:	
lemark on P	The additional search fees were accompanied by the applicant's protest.	
	N protest accompanied the payment of additional search fees.	

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-7,9 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds specifically mentioned in the claims, with due regard to the general idea underlying the present application.

Present claims 1-9 relate to compounds defined by reference to a desirable characteristic or property, namely immunosuppressant property. The claims cover all compounds/uses having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the products/compounds specifically mentioned in the claims.

The Present claims 1-9 relate to a method/use defined (inter alia) by reference to the following parameter(s): P1: MMP production inhibitor/ treating MMP-mediated disease. The use of these parameters in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art. The lack of clarity is such as to render a meaningful complete search impossible. Consequently, the search has been restricted to the "More preferable MMP-mediated diseases" (Cf. page 15 of the description), with due regard to preferable MMP-mediated diseases.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

on on patent family members

onal Application No PCI/JP 99/04978

and the particular of the part			re1/J	P 99/04978		
	atent document d in search repo		Publication date		Patent family member(s)	Publication date
WO	9117754	Α	28-11-1991	NOI	VE .	-
WO	9811908	Α	26-03-1998	AU.	4390597 A	14-04-1998
				EP	0936918 A	25-08-1999
WO	9318048	Α	16-09-1993	AT	159725 T	15-11-1997
				CA	2131373 A	16-09-1993
				DE	69314947 D	04-12-1997
				DE DK	69314947 T 636136 T	05-03-1998
				EP	0636136 A	22-12-1997 01-02-1995
				ES	2108261 T	16-12-1997
				FI	944015 A	01-09-1994
				GR JP	3025672 T 7500350 T	31-03-1998
				JP	7500350 T 2562001 B	12 - 01-1995 11 - 12-1996
				ÜS	5631235 A	20-05-1997
WO ·	9318050	Α	16-09-1993	A T		
	J010030	^	10-09-1993	AT CA	153027 T 2131372 A,C	15-05-1997
				DE	69310721 D	16-09-1993 19-06-1997
	•			DE	69310721 T	04-09-1997
				DK	629209 T	13-10-1997
				EP ES	0629209 A	21-12-1994
				FI	2102642 T 944017 A	01-08-1997 01-09-1994
				GR	3024048 T	31-10-1997
				JP	2563080 B	11-12-1996
				JP	7500352 T	12-01-1995
				MX US	9301060 A 5747465 A	01-09-1993 05-05-1998
DE 4	1329503	A	02-03-1995	AU	693470 B	
				AŬ	7535494 A	02-07-1998 22-03-1995
				CA	2170748 A	09-03-1995
				WO	9506464 A	0 9- 03-1995
				EP JP	0716598 A 9501939 T	19-06-1996
				NZ	271655 A	25-02-1997 22-09-1997
US 5	352671	Α	04-10-1994	US	5912238 A	 15 - 06-1999
				AT	126803 T	15-09-1995
				ΑU	640963 B	09-09-1993
				AU Ca	6584390 A	23-05-1991
				DE	2029694 A 69021833 D	10-05-1991 28-09-1995
				DE	69021833 T	21-03-1995
				DK	427680 T	18-12-1995
				EP ES	0427680 A	15-05-1991
				ES Gr	2077663 T 3017858 T	01-12-1995 31-01-1996
				HK	30096 A	23-02-1996
				HU	210900 B	28-09-1995
				ΙE	69974 B	16-10-1996
				TI	06060 #	
				IL JP	96268 A 2750302 B	23-07-1996
				IL JP JP	96268 A 2750302 B 3223291 A	

tion on patent family members

lonal	Application No	
TeT/JP	99/04978	-

Patent document cited in search report	Publication date		Patent family member(s)	Publication date
US 5352671 A		LV LV NZ ZA	11621 A 11621 B 235991 A 9009024 A	20-12-1996 20-04-1997 26-05-1993 29-07-1992

Form PCT/ISA/210 (patent family annex) (July 1992)